REMARKS

This amendment is largely in response to the Final Office Action in this case. In that Office Action the Examiner renewed the rejections of Claims 1-4, 6-9, and 14-16 under 35 U.S.C. §103(a) as being unpatentable over **Lin et al.** (U.S. Patent No. 5,459,030) and **Shanbrom** (U.S. Patent No. 5,985,260) or **Shanbrom** (WO 9822151) or **Piechocki et al.** (U.S. Patent No. 5,660,731) for obviousness. The Examiner also renewed his rejection under 35 U.S.C. §103(a) based on **Gluck** (WO 8900006). The Examiner objected to Claims 5 and 10 as being based on rejected base claims.

Applicant apologizes for overlooking the rejections based on **Gluck** in the prior amendment. That rejection is addressed below.

Before the present amendment Claims 1-16 were in prosecution. According to this amendment Claims 2, and 14-16 have been cancelled. Claims 1,3-5, 7-10 and 13 have been amended. New Claims 17-25 have been added. Claims 1, 3-13 and 17-25 are now in prosecution.

The present invention is based on the surprising discovery that increased amounts (as compared to the 0.4% routinely used as an anticoagulant for blood) of citric acid and or citric acid salts shows significant antimicrobial activity especially when combined with other antimicrobial materials. The inventor calls this property "enhancement" and theorized that some common mechanism is responsible for this

effect on a variety of antimicrobial agents. However, there is as yet no proof that all the reported effects share a common mechanism. In the original claims the lumping together of disparate antimicrobial substances was in response to this theory but may have, in fact, obscured Applicant's arguments in favor of patentability. The different antimicrobial substances have now been claimed separately so that they can be discussed and argued separately. This separation was achieved by adding new claims and amending existing claims. Most of the claim amendments resulted from the separate claiming of the microbial agents. In a few instances amendments were made to correct errors and inconsistencies in the original claims.

Amended Claim 1 now claims a method of enhancing the antimicrobial properties of an antibiotic by adding at least 1% of citric acid and or salts of citric acid to the antibiotic. Applicant respectfully contends that none of the cited references disclose or suggest in any way that citric acid significantly enhances the antibacterial properties of antibiotics. This is in spite of the extremely strong motivation to discover methods to augment the activity of existing antibiotics especially in the face of the increasing numbers of antibiotic resistant microbes. The Examiner will note that data presented in the specification clearly demonstrate that citric acid causes antibiotics to become effective even against antibiotic resistant organisms. Applicant respectfully requests that the rejection of Claim 1, as now amended, be withdrawn.

New Claim 17 is now directed to the enhancement of the antimicrobial properties of disinfectant organic dyes by increased levels of citric acid or citric acid salts. The significant point to the current invention, a point not stressed in the original claim, is that the citric acid enhances the effectiveness of disinfectant dyes without exposure to light. The present invention is not at all dependant on light activation of the dye. While it is likely that light might further increase the effectiveness of citrate, that step is not necessary to the present invention. On the other hand, the **Piechocki et al.** reference describes a method for removing a photoactive agent. Essentially, this reference teaches the well-known use of light to transform a dye (methylene blue) into a microbicide. That use requires elaborate devices to ensure uniform and strong exposure of the treated blood to light. Without photoactivation methylene blue cannot sufficiently kill or inhibit microorganisms. There is no suggestion in **Piechocki et al.** that citric acid in any way affects this process. Nor is there any suggestion that disinfection can be achieved without light by adding sufficient citric acid. In the absence of any suggestions that altering the citric acid level has any effect whatsoever Applicant respectfully submits that producing significant disinfectant dye mediated killing of microbes without a photoactivation step (see table on page 10—note that dye alone causes some inhibition of the bacteria but dye plus citrate completely prevents bacterial growth) does represent an unexpected result. Therefore, Applicant respectfully submits that new Claim 17 is allowable over the cited prior art.

Claim 4 is now directed to a method of using citrate levels above 1% to prevent bacterial growth in platelet concentrates while Claim 9 is a similar method for use on red blood cells. The Examiner previously cited **Lin et al.** as teaching or rendering obvious such uses of citrate. Applicant respectfully traverses this rejection. **Lin et al.** teach a method of photoinactivation of bacteria employing psoralens. There is no teaching that the inclusion of sodium citrate in the medium enhances the effect of the photoinactivation. Rather, citrate is included as a buffer and/or anticoagulant. Applicant notes that all of the formulae of Lin et al. contain substantially less than 1% citrate and all contain some type of psoralen. A major objective of **Lin et al.** is to reduce the amount of light energy and psoralen needed to inactivate bacteria. Currently, it is unknown whether increased levels of citrate would enhance the psoralen effect. If, as the Examiner contends, routine "optimization" would lead to use of a high level of citrate, **Lin et al** is a good reference for rendering the combination of high levels of citrate and psoralen obvious. However, the instant invention does not employ psoralen. With the claims now amended to make this clear, Applicant respectfully requests the Examiner to withdraw the rejection of Claims 4 and 9 based on **Lin et al.**

Claim 19 is directed to using citrate to enhance the antimicrobial effectiveness of iodine without use of an iodophor. The Examiner has cited two of the inventor's own patents against this use. However, neither of the two **Shanbrom** references specifically refer to use of citrate. Further, the PCT reference is primarily directed to

the removal of iodine after disinfecting a solution. Because citrate is often used as an anticoagulant (at about 0.4%) it is possible that some of the experiments described in those references might have contained that level of citrate. However, that is below the level of citrate required to observe any enhancement of the disinfecting effect. Please note that data in the specification (pages 13 et seq.) show a significant increase in the effectiveness of iodine disinfection resulting from addition of citrate. Applicant respectfully contends that this is the type of unexpected result the Examiner requests.

The Examiner also cited **Gluck** as employing a variety of organic acids, including citrate to enhance the effects of iodine. Applicant respectfully points out that **Gluck** actually teaches the use of an iodophor with an iodine liberating substance and an oxidizing compound (see page 3, first three paragraphs). All forms of the **Gluck** invention employ iodophors since the object is to produce an iodine/iodophor solution wherein the ratio of iodophor to iodine is less than 5:1. Thus, this reference does not apply to Claim 19 which specifically eschews the use of an iodophor. Claim 20 does include an iodophor but specifically eliminates any oxidizing substance (other than iodine itself). Thus, the composition of Claim 20 could not work like the **Gluck** invention since it has no iodine liberating substance. **Gluck** does not teach the use of acids such as citric acid without an added oxidizing agent. Nor is there anything in the reference to even suggest that there is any reason to employ such an acid without an oxidizing agent. The reference makes it clear that

the sole effect of the citrate is to adjust the pH of the solution. There is no teaching or suggestion that citrate enhances the germicidal effectiveness of the mixture. Therefore, Applicant respectfully contends that both Claims 19 and 20 are allowable over the art of record.

The additional new claims are directed towards a topical composition as was original Claim 14.

If for any reason the Examiner still finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (310) 734-5403 to discuss the steps necessary for placing the application in condition for allowance. You are hereby authorized to charge any fees due and refund any surplus fees to our Deposit Account No. 50-1796, referencing docket number 25864.05500.

Respectfully submitted,

CROSBY, HEAFEY, ROACH & MAY

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Marked-up Claim Copy (Revised Rule 121)

1. (Twice Amended) A method for enhancing the antimicrobial effectiveness of [antimicrobial agents] an antibiotic comprising the step of combining the [antimicrobial agent] antibiotic with at least 1% by weight citric acid and or salts [or] of citric acid.

3. (Once Amended) The method of Claim [2] 17, wherein the disinfectant organic [dyes are] dye is selected from the group consisting of methylene blue, [and] crystal violet, and mixtures thereof.

4. (Once Amended) A method for extending the life of a platelet concentrate and preventing the multiplication of bacteria therein comprising the step of adding between 1 and 15% by weight of [sodium citrate] citric acid and or salts of citric acid to the platelet concentrate, wherein essentially no psoralen is present.

5. (Once Amended) The method of Claim 4, further comprising the step of removing the [sodium citrate] citric acid and or salts of citric acid.

7. (Once Amended) The method of Claim 4[, wherein the] further comprising the step of adding an antimicrobial agent is selected from the group consisting of antibiotics, povidone iodine, iodine, polyphenols of plant origin, and disinfectant organic dyes.

8. (Once Amended) The method of Claim 7, wherein the disinfectant organic dyes are selected from the group consisting of methylene blue, [and] crystal violet, and mixtures thereof.

9. (Once Amended) A method for disinfecting solutions containing red blood cells comprising the step of adding between 1 and 15% by weight of [sodium citrate] citric acid and or salts of citric acid to the solution, wherein essentially no psoralen is present.

10. (Once Amended) The method of Claim 9, further comprising the step of removing the [sodium citrate] citric acid and or salts of citric acid.

13. (Once Amended) The method of Claim 12, wherein the disinfectant organic dyes are selected from the group consisting of methylene blue, [and] crystal violet, and mixtures thereof.